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<b>(21) International Application Number:</b> PCT/US92/10839 <b>(22) International Filing Date:</b> 15 December 1992 (15.12.92)  <b>(30) Priority data:</b> 937,464 28 August 1992 (28.08.92) US 973,263 9 November 1992 (09.11.92) US  <b>(71) Applicant:</b> CORTRAK MEDICAL, INC. [US/US]; 2660 Patton Road, Roseville, MN 55113 (US).  <b>(72) Inventors:</b> HILDEBRAND, Keith, R. ; 422 Highland View, Houlton, WI 54082 (US). RACCHINI, Joel, R. ; 4221 West 44th Street, Edina, MN 55424 (US). SHAPLAND, James, E. ; 4322 Rustic Plane, Shoreview, MN 55126 (US). SHIMADA, Jin ; 1839 Simpson Street, Falcon Heights, MN 55113 (US). KNUDSON, Mark, B. ; 1309 West Royal Oaks Drive, Shoreview, MN 55126 (US).		<b>(74) Agent:</b> ROTHFUS, Joel, A.; Merchant, Gould, Smith, Edell, Welter & Schmidt, 1000 Norwest Center, 55 East Fifth Street, St. Paul, MN 55101 (US).  <b>(81) Designated States:</b> AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> POLYMER MATRIX DRUG DELIVERY APPARATUS AND METHOD  <div style="text-align: center;"> </div> <b>(57) Abstract</b>  A drug delivery apparatus and method for delivering a drug locally to internal body tissue using a catheter device including a polymer matrix (12) containing a drug. The drug is actively transported from the polymer matrix (12) to the internal body tissue using iontophoresis or phonophoresis. In addition, the polymer matrix (12) can be expanded to promote intimate contact with the walls of a passageway or vessel.		

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**POLYMER MATRIX DRUG DELIVERY APPARATUS AND METHOD****BACKGROUND OF THE INVENTION****1. Field of the Invention**

5           The present invention relates to a drug  
delivery apparatus and method for selectively and  
locally delivering a drug to internal body tissue. More  
particularly, the present invention relates to a  
catheter device including a polymer matrix containing a  
10 drug and transport means for actively transporting the  
drug from the polymer matrix to the internal body  
tissue.

**2. Description of the Related Art**

15           Many techniques currently exist for delivering  
drugs or other medicaments to body tissue. These  
include, among possible others, oral administration,  
injection directly into body tissue such as through an  
intramuscular injection or the like, topical or  
20 transcutaneous administration where the drug is  
passively absorbed, or caused to pass, into or across  
the skin or other surface tissue and intravenous  
administration which involves introducing a selected  
drug directly into the blood stream.

25           Except for topical or transcutaneous  
administration, the above drug delivery systems tend to  
be systemic. In other words, administration of the drug  
is delivered throughout the body by the blood stream.  
Although transcutaneous drug delivery systems tend to be  
30 localized delivery systems in that the drug is delivered  
locally to a selected area, such drug delivery systems  
are also, by definition, limited to application of a  
drug externally through the patient's skin or other  
surface tissue. Thus, the above described drug delivery  
35 systems are generally not appropriate for the localized  
treatment of internal body tissue.

Because of the limitations of transcutaneous  
drug delivery systems along with the problems associated  
with systemic drug administration, the benefits of

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devices providing localized internal delivery of drugs have become more apparent. In particular, localized internal delivery devices avoid the high dosage levels associated with systemic delivery which can result in adverse side effects. Systemic delivery also fails to concentrate the therapeutic agents in the local area where they are most effective. In addition, by treating only the diseased tissue with a localized delivery device, the total quantity of drug used may be significantly reduced which also reduces the cost of therapy. Furthermore, localized drug delivery may also allow the use of therapeutic agents which, although very effective, have previously been considered too toxic or non-specific to administer systemically.

One example is the ability to treat the dilated vessel in percutaneous transluminal coronary angioplasty (PTCA), and thus limit or prevent restenosis. In PTCA, catheters are inserted into the cardiovascular system under local anesthesia and an expandable balloon portion is then inflated to compress the atherosclerosis and dilate the lumen of the artery. Despite the general success of such PTCA procedures, high restenosis rates (reported to be as high as 47%) continue to be a major problem. Various techniques have been tried to treat stenosed vessels including the use of lasers, application of heat and the use of intravascular stents. However, many of these are still under investigation with mixed results, while others have generally not been successful. The ability to administer a drug locally to the dilated portion of the artery in PTCA procedures, without significantly affecting other tissues, would greatly enhance the ability to address the restenosis problem.

A second example of specific application for a local drug delivery system for delivering a drug to an internal body tissue is in the treatment of cancerous tumors or the like. In the treatment of such tumors, an

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objective is to administer the cancer drug so that it localizes, as much as possible, in the tumor itself. Such drugs are commonly administered systemically through the blood stream. Various means are then  
5 utilized for causing the drug to localize in the cancer tumor. Nevertheless, significant portions of the drug still circulate through the blood stream, thereby affecting non-cancerous tissue, producing undesirable side effects, and limiting the dosages of the drug which  
10 can be safely administered.

Catheter based drug delivery systems to accomplish the above procedures have been developed. Double balloon catheters have been used to administer agents to the area confined by the balloons in a vessel  
15 or other body passageway. That system, however, has the disadvantage in that drugs may be lost through communicating vessels between the balloons. In addition, a perforated balloon has been used to deliver drug solutions under pressure across a porous balloon  
20 wall and directly into a hollow organ.

Although the catheter-based local drug delivery systems are somewhat effective, they are typically designed to deliver therapeutic agents in solution. That limitation is the source of several disadvantages.

25 First, the desired therapeutic agent must be readily soluble in an appropriate solvent. Many drugs are not, however, easily solubilized in aqueous-based solvents.

Second, the catheters must be equipped with  
30 conduits to introduce and possibly evacuate the liquid solution, as well as a terminal drug reservoir. Such devices typically use inflatable balloons which either act as drug reservoirs or restrict drug movement to a specific segment of the vessel or hollow organ. In  
35 addition to the conduits needed to introduce and evacuate the liquid drug solution, one or more conduits must also be provided to inflate and deflate the

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catheter balloon. Multiple conduits such as those described above not only add to the complexity and cost of the catheter, but also increase its profile, thereby limiting the applications for which it can be used.

5 Third, because fluids are being delivered there is the risk of leakage from a defective or damaged conduit or balloon. Leakage can result in a serious overdosage or, may simply waste a valuable medication which is targeted for local delivery.

10 Fourth, the liquid drug solution must be prepared and introduced into the catheter by the physician. Such procedures add time, complication and expense to the use of these devices and are also more likely to result in the administration of inaccurate  
15 dosages.

United States Patent No. 5,102,402 to Dror et al. discloses the use of drugs contained in micro-capsules located on the outer surface of a balloon catheter. The capsules are ruptured using sonic energy.  
20 Upon rupturing, the capsules deliver the drug internally. This patent does not, however, disclose the use of phonophoresis to actively transport the drugs into the surrounding tissue. Instead, the drug is delivered through passive diffusion, thereby limiting  
25 its penetration.

Accordingly, there is a need in the art for a method and apparatus for active delivery of a drug that is not in liquid solution selectively and locally to internal body tissue, without significantly affecting  
30 other tissue. There is a further need for such a system and method for the localized treatment of internal body tissues to limit restenosis following PTCA, to treat cancerous tumors or the like, or to treat various other medical situations.

35 SUMMARY OF THE INVENTION

In accordance with the present invention, an apparatus and method is provided for active delivery of

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a drug or combination of drugs selectively and locally to an internal body tissue using a polymer matrix incorporated into a catheter-based delivery system. The invention involves an apparatus and method for active  
5 delivery of a drug or combination of drugs substantially transversely to the longitudinal axis of a body passageway such as blood vessel, urinary tract, intestinal tract, reproductive tract, etc., to treat a localized region of the passageway itself or to treat a  
10 localized region or tissue located adjacent to the passageway. The invention also involves an apparatus and method for active delivery of a drug or combination of drugs directly to an internal body tissue.

In the preferred embodiment, the apparatus  
15 includes a flexible member adapted for insertion into the body passageway or tissue and a drug delivery means connected with the flexible member for delivering the drug to or through a local area of the passageway wall or tissue. The drug delivery means includes a drug  
20 incorporated into a polymer matrix. Also included is transport means associated with the drug delivery means for actively transporting the drug out of the polymer matrix to the area to be treated. The transport means is typically iontophoresis or phonophoresis.

25 The method of the present invention involves positioning a drug delivery member, including a polymer matrix containing a drug, in a body passageway such that the delivery member traverses the desired localized area of administration. After the drug delivery member is in  
30 place, the drug is actively transported out of the polymer matrix for delivery to the desired area of the passageway. The method for delivering a drug to an internal body tissue involves positioning the drug delivery component at a target area of an internal body  
35 tissue and actively transporting the selected drug from the polymer matrix into the internal body tissue target area.

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Polymer matrixes incorporating drugs have been previously employed as implantable slow sustained release devices. The present invention, however, adds an active transport means, i.e., either iontophoresis or  
5 phonophoresis, to rapidly and effectively transport the drugs from the polymer matrix into the targeted area.

The present invention also solves many of the disadvantages associated with known catheter-based local internal drug delivery systems. Because the drug is not  
10 in liquid form, the need for conduits to deliver and evacuate the drug solution is also eliminated. That can help limit the profile, and cost, of the catheter. The matrix is pre-loaded with a known quantity of medication and delivered by an active transport means such as  
15 iontophoresis or phonophoresis which allows for precise and controlled drug delivery. The polymer matrix also eliminates the chance of leakage of the drug solution and the resulting problems associated with those occurrences. Finally, because the drug is pre-loaded  
20 into the polymer matrix, the catheter can be inserted without any need for preparing, filling or circulating a drug solution through the catheter, also saving time and simplifying usage.

These and other advantages of the present  
25 invention will become apparent with reference to the drawings, the description of the preferred embodiments and methods and the appended claims.

#### DESCRIPTION OF THE DRAWINGS

Figure 1 is a fragmentary view, partially in  
30 section, of a first embodiment of the drug delivery apparatus of the present invention in the form of a catheter with a polymer matrix and transport means before expansion.

Figure 2 is a fragmentary view, partially in  
35 section, of the drug delivery apparatus of Figure 1 with the transport means located within the polymer matrix.



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Figure 3 is a fragmentary view, partially in section, of the apparatus of Figure 1, after removal of the transport means from the polymer matrix.

Figure 4 is a partial cross-section of a further embodiment of the drug delivery apparatus of the present invention.

Figure 5 is a partial cross-section of the embodiment of Figure 4 with the polymer matrix expanded.

Figure 6 is a partial cross-section of the embodiment of Figures 4 and 5, with the catheter prepared for removal.

Figure 7A is a schematic representation of a manually-loaded wire basket electrode for use in the present invention.

Figure 7B is a schematic representation of the manually-loaded wire basket electrode of Figure 7A in its expanded state.

Figure 8A is a partial cross-sectional view of a further embodiment of the drug delivery apparatus of the present invention incorporating a balloon to expand the polymer matrix and an expandable electrode placed between the balloon and the polymer matrix.

Figure 8B is a partial cross-sectional view of the catheter of Figure 8A in its expanded state.

Figure 9A is a partial cross-sectional view of a further embodiment of the drug delivery apparatus of the present invention incorporating a balloon for expansion and a central electrode.

Figure 9B is a partial cross-sectional view of the catheter of Figure 9A in its expanded state.

Figure 10 is a partial cross-sectional view of a further embodiment of the drug delivery apparatus of the present invention incorporating a balloon for expansion and a transducer for phonophoresis.

Figure 11 is a partial cross-sectional view of a further embodiment of the drug delivery apparatus of the present invention designed for use in internal

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tissue where expansion of the polymer matrix is not needed to provide intimate contact.

Figure 12A is a view of a further embodiment of the drug delivery apparatus of the present invention incorporating a movable sheath for protection of the polymer matrix.

Figure 12B is a view of the catheter of Figure 12A with the sheath retracted and the polymer matrix exposed for drug delivery.

Figure 13 is a view of a further embodiment of the drug delivery apparatus of the present invention incorporating a porous outer membrane for protection of the polymer matrix.

DESCRIPTION OF THE PREFERRED  
AND ALTERNATE EMBODIMENTS AND METHODS

Figures 1-13 illustrate the preferred and various alternate designs of the drug delivery apparatus in accordance with the present invention. In general, this apparatus provides a means and a system for delivering a drug or combination of drugs to or through a localized area of a passageway to treat the localized area of the passageway or to treat a localized area of tissue located adjacent to the passageway, with minimal, if any, undesirable effect on other body tissue. The term catheter as used in the present application is intended to broadly include any medical device designed for insertion into a body passageway to permit injection or withdrawal of fluids, to keep a passage open or for any other purpose. It is contemplated that the drug delivery apparatus of the present invention has applicability for use with any body passageways including, among others, blood vessels, urinary tract, intestinal tract, reproductive tract, respiratory tract and the like.

Many of the embodiments are also capable of delivering a drug or combination of drugs to a localized area of an internal body tissue. For this purpose the apparatus includes a flexible catheter connected to a

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drug delivery component having a polymer matrix surrounding a transport means. The transport means is used to actively transport the drug from the polymer matrix to an internal body tissue target area.

5 Catheters are commonly used in percutaneous transluminal coronary angioplasty (PTCA) procedures to dilate stenosed blood vessels or arteries. These include "over-the-wire" catheters of the type illustrated generally in U.S. Patent No. 4,323,071, the  
10 disclosure of which is incorporated herein by reference, and "fixed-wire" catheters of the type illustrated in U.S. Patent No. 4,582,181, the disclosure of which is also incorporated herein by reference. These catheters may be modified according to the present invention.

15 To illustrate the method aspect of treating a localized area of a passageway, the specific application of the present invention to the reduction of restenosis will be described. Following a discussion of reducing restenosis, the present invention will be applied to the  
20 treatment of tumors.

As indicated above, percutaneous transluminal coronary angioplasty (PTCA) has been demonstrated to be a highly successful procedure for the treatment of atherosclerosis and other diseases and conditions  
25 tending to narrow arterial passageways. In normal PTCA procedure, a dilatation catheter is advanced along an artery to the desired position in the arterial system. The catheter includes an inflatable balloon at its distal end and means for inflating the balloon. When  
30 the balloon is positioned so that it traverses or crosses a stenotic lesion, the balloon is inflated to compress the atherosclerosis and expand the artery in a direction generally perpendicular to its wall, thereby dilating the lumen of the artery. Following this  
35 procedure, the balloon is deflated and the catheter withdrawn.

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Despite the generally excellent success of PTCA, relatively high restenosis (the tendency of the dilated artery to close) rates continue to be a major problem. Restenosis can include abrupt reclosure  
5 resulting from thrombotic occlusion, vasospasms, or the like as well as the more common occurrence of gradual restenosis.

In accordance with the method of the present invention, a drug referred to as a fixation solution or  
10 a fixative is delivered locally to the dilated portion of the vessel to render the vessel wall biologically inert to prevent or reduce reactions that lead to reclosure. Because of the nature of the fixative and its ability to inactivate living cells and render the  
15 tissue in which it comes into contact biologically inert, it is essential that such fixative be exposed only to that portion of the arterial wall which has been dilated.

A preferred method and apparatus for delivering  
20 the fixative locally to the dilated vessel is via a catheter modified according to the present invention. The catheter that delivers the drug may be the same catheter that dilates the vessel, thus combining both functions in one catheter. Alternatively, a vessel may  
25 be dilated first with a catheter designed specifically for dilation, followed by insertion of a second catheter for drug delivery. Modified catheters useful for either approach is illustrated in Figures 1-3, 8 or 9, all of which are described in detail below.

30 Figure 1 illustrates the distal end of a catheter. The catheter includes an elongated, flexible catheter body 11, a drug delivery means in the form of a drug-impregnated polymer matrix 12 positioned in the catheter body 11 near its distal end.

35 In the embodiment illustrated in Figure 1, impermeable end caps 17 are located on either end of the substantially cylindrical polymer matrix 12 to prevent

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movement of the drug in the matrix 12 longitudinally along the catheter body 11. The end caps 17 are, however, optional and may be added or removed as desired depending on the extent of leakage in the axial  
5 direction during drug transport and any undesirable effects that the leakage may have on the patient.

An electrode passageway 14 extends along the catheter body 11 on either side of the polymer matrix 12. A wire 16 is attached to the electrode 18 which is  
10 positioned in the distal end of passageway 14. The wire 16 extends from the proximal end of the catheter body 11 to its distal end where it is attached to electrode 18.

As used in the embodiments described with respect to Figures 1-10 in the present invention (all of  
15 which are designed to expand radially), the polymer matrix material used as the drug reservoir should be a compliant and expandable material that is, ideally, also non-compressible or minimally compressible. The material must be compliant and expandable to allow  
20 sufficient expansion of the polymer matrix material by the expansion means, whether the expansion means is an electrode 18 as in Figure 1, wire basket 56 as in Figure 5, wire basket 70 as in Figure 7A or balloon 86 in Figure 8.

25 The compressibility of the material is preferably limited to maximize the diameter of the catheter when the polymer matrix material is expanded, thus ensuring intimate contact between the polymer matrix and target tissue to enhance drug transfer. It  
30 is also contemplated that the polymer matrix material could be compressible, provided that the expansion means is designed to ensure intimate contact in spite of the compressibility of the polymer matrix material.

In the embodiments which do not expand  
35 radially, one of which is illustrated in Figure 11, it will be understood that the polymer matrix material need

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not be expandable or non-compressible and may, in fact, be rigid if desired.

As used in conjunction with the present invention, the term "polymer matrix" includes synthetic polymers in the form of hydrogels or other porous or drug-permeable configurations or morphologies, such as polyvinyl alcohol, polyvinylpyrrolidone and polyacrylamide, polyethylene oxide, poly(2-hydroxy ethyl methacrylate); natural polymers such as gums and starches; synthetic elastomers such as silicone rubber, polyurethane rubber; and natural rubbers. The above examples are provided for reference only, and the range of suitable polymer matrix materials should not be construed as limited to those materials listed above.

The polymer matrix material can also be hydrophilic or hydrophobic, provided it meets the physical characteristics described above.

Drugs may be incorporated into the polymer matrix material by a variety of methods. The drug can be incorporated into the material as the polymer solution or dispersion is formed into the preferred annular shape; it can be added to the polymer matrix material after formation into the desired shape either passively or actively (through, for example, such methods as iontophoresis); the drug can be dissolved in a solvent (e.g., water, propylene, glycol, etc.) and the resulting solution can be incorporated into the polymer matrix material; or the drug molecules can be incorporated directly into the polymer matrix material.

Figure 2 illustrates the drug delivery apparatus of Figure 1 with the polymer matrix 12 in its expanded state within an arterial vessel with walls 15. During PTCA procedures, the catheter including the catheter body 11 and polymer matrix 12 is advanced to the desired position in the arterial system in which the polymer matrix 12 traverses or crosses the stenotic lesion. The matrix 12 is then expanded by pulling the

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electrode 18 into the interior chamber 13 of the polymer matrix 12. Wire 16 is preferably attached to a handle (not shown) at the proximal end of the catheter to allow electrode 18 to be pulled into the matrix 12. As a  
5 result, wire 16 is used to move electrode 18 into position in the matrix 12 (thereby expanding the matrix) as well as providing current to electrode 18 after the electrode is in place.

After expansion, the outer surfaces of the  
10 polymer matrix 12 press outwardly against the inner surfaces of the vessel wall 15 to expand or dilate the vessel in the area of the stenotic lesion. The fixative or other drug in the matrix 12 is then transported into the surrounding tissue using iontophoresis.

15 Alternatively, catheters according to the present invention may be used to perform dilation of the vessel as well as deliver the fixative or other drug to the targeted tissue.

In general, the preferred drug transport means  
20 is iontophoresis, which uses an electrical potential or current to drive ionic fixatives or drugs or drug nonionic fixatives or drugs in an ionic solution. Iontophoresis is useful in the present invention because it facilitates both transport of the fixative or drug  
25 out of the polymer matrix 12 and tissue penetration.

In iontophoresis, two electrodes are used to develop the required potential or current flow. In particular, one electrode 18 (the "catheter electrode") is located inside of the polymer matrix 12 while the  
30 other electrode is preferably located at a remote site on a patient's skin. The other electrode may also, in certain applications, be positioned at other regions of the patient, including appropriate internal areas and may, in fact, also be located along the catheter body at  
35 a site removed from catheter electrode 18.

In addition to constant direct current, other waveforms may be used (e.g., a series of rectangular

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waves producing a frequency of 100 Hz or greater) to accomplish the iontophoretic delivery process. A more complete description of iontophoresis and the alternate direct current waveforms useful in conjunction with the present invention can be found in U.S. Patent Application S/N 07/957,209, filed on October 6, 1992, titled INTERNAL IONTOPHORESIS ELECTRICAL CIRCUIT AND WAVEFORMS, by James E. Shapland and Keith Hildebrand, which is hereby incorporated by reference.

For iontophoresis techniques to be used, the fixative or other drug within the polymer matrix 12 should have specific characteristics. Ideally, the fixative or other drug should have an ionic nature or have other ionic molecules bound to the fixative or the active components of the drug to promote the iontophoretic movement or transport from the polymer matrix 12. An electrical current for the iontophoretic process of Figure 2 is produced between the electrodes 18 and 20 by an external power source 30 through the electrical leads 22 and 24, respectively.

In addition to drug delivery to internal tissue, the polarity of the iontophoretic electrodes may be reversed after treatment to recapture excess fixative or drug delivered to or through the vessel wall.

As described above, a fixative or fixation agent is a compound or composition known in the art as a fixative. A fixative functions, among other things, to kill, penetrate and harden fresh tissues, to set the tissues so that they will not be altered by subsequent biological or other processing and to render the cell constituents insoluble. Fixatives are commonly used for stabilizing and fixing tissue at the moment such tissue is exposed to the fixative so that histologic slides of the tissue can be prepared or the tissue can otherwise be preserved for examination.

The particular fixative or fixation solution as contemplated for use with the present invention should



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rapidly penetrate the plaque and vascular tissue of the vessel in the area of the stenotic lesion. It should quickly kill or otherwise preserve the tissue, while hardening the vascular structure. Such fixation

5 maintains the vessel in an "opened" or dilated condition and prevents or substantially reduces reclosure due to vasospasm or other abrupt reclosure mechanisms. Such fixation also retards or stops the biological processes which lead to gradual restenosis. The preferred

10 fixative should also have rapid, specific action in high concentrations, and generally nontoxic actions in lower concentrations.

After transport of the fixative or drug from the polymer matrix 12 is completed, the electrode 18 is

15 removed from the polymer matrix 12 and is preferably pulled into holding chamber 19 using wire 16 as shown in Figure 3. Removing electrode 18 from polymer matrix 12 allows the matrix to assume its narrower profile which aids in removal of the catheter from the vessel.

20 It will be understood by those skilled in the art that electrode 18 could also be stored in its original holding chamber 14 if a means of pushing electrode 18 into that chamber after use is provided. In the preferred embodiment however, the wire 16 used to

25 supply power to the electrode 18 cannot supply a compressive force sufficient to push electrode 18 out of the polymer matrix 12. As a result, holding chamber 19 is used to store the electrode after wire 16 is used to pull electrode 18 into holding chamber 19.

30 Figures 4-6 depict an alternative embodiment of a catheter constructed according to the present invention. The primary difference between this catheter and the catheter of Figures 1-3 is the use of a spring loaded wire basket 56 which, prior to use, is stored in

35 a holding chamber 48 constructed in catheter body 46. Construction of the polymer matrix 42 is substantially

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similar to that described with respect to the embodiment of Figures 1-3.

The polymer matrix 42 is provided in catheter body 46 in a substantially cylindrical shape. As with the preferred embodiments described above, optional impermeable end caps 43 are provided at either end of the polymer matrix to prevent transport of the drug contained in the polymer matrix 42 axially along the catheter body 46. The polymer matrix 42 is also provided with an interior cavity 50 for receiving the spring loaded basket 56. Opposite holding chamber 48 in catheter body 46 is holding chamber 52 which is used to store the spring loaded basket 56 after expansion of the polymer matrix 42. Storage of the compressed wire basket 56 in holding chamber 52 is depicted in Figure 6.

In the preferred embodiment, spring loaded basket 56 also serves as an electrode for iontophoretic drug transport in addition to being used to expand the polymer matrix 42. Wire 54 provides electric current to the basket 56 during the iontophoresis process as well as moving the basket 56 between holding chamber 48, cavity 50 in polymer matrix 42 and holding chamber 52.

Referring to Figures 4-6, in use spring loaded basket 56 is drawn into chamber 50 in the polymer matrix 42 where it expands the polymer matrix. After expansion, the transport process is begun wherein current is provided to the electrode/spring loaded basket 56 via wire 54 to transport the fixative or other drug from the polymer matrix 42 to the appropriate area. After the transport process is completed, the spring loaded basket is drawn further through the catheter body 46 into holding chamber 52 which allows the polymer matrix 42 to return to its narrower profile by compressing the spring loaded basket 56, thus aiding removal of the catheter from the vessel.

As with the embodiment depicted in Figures 1-3, the basket 56 is pulled into position using a wire 54

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which is also used to provide current to the basket 56 during iontophoresis. As such, wire 54 cannot apply sufficient force to basket 56 to return it to cavity 48 after use. It will, however, be understood that if an appropriate mechanism to do so is used, chamber 52 would be unnecessary.

Figures 7A and 7B depict an alternate embodiment of the wire basket design for use in the embodiments depicted in Figures 4-6. The basket 70 differs from the basket 56 of the embodiment depicted in Figures 4-6 in that it is manually-loaded as opposed to being spring-loaded. If a manually loaded basket 70 is used, it will be understood that holding chambers 48 and 52 depicted in Figures 4-6 would not be required as the basket would be manually expanded or relaxed as desired by the user.

Figure 7A depicts the manually-loaded basket 70 in its relaxed or unexpanded state while Figure 7B depicts the basket 70 in its expanded position. The basket is expanded by the use of force along wire 72 which extends through the basket to its distal end 74. The connection of the basket at point 76 along wire 72 is essentially a slip fit which allows point 76 to move along wire 72 when a force is applied to wire 72. As a result, the distance between points 74 and 76 is shortened, which translates into expansion of the diameter of the basket 70.

As with the spring-loaded basket, the manually loaded basket 70 also serves as the electrode when iontophoresis is used to supply the transport mechanism to transport drugs or fixatives from the polymer matrix to the appropriate area.

One advantage of the manually-loaded basket 70 is the ability of the user to control the amount of expansion of the basket 70 by pulling a specific length of wire 72 from the catheter. In the preferred embodiment, the wire 72 is supplied with appropriate

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markings along its length to indicate expansion of the basket 70.

The polymer matrix of the present invention can also be used in conjunction with a balloon to supply force to enlarge a vessel wall and/or provide intimate contact between a drug-impregnated polymer matrix and the vessel wall. Referring to Figures 8A and 8B, the embodiment depicted there includes a polymer matrix 82 located along a section of catheter body 80. Optional impermeable end caps 83 are located on either end of the substantially cylindrical polymer matrix 82 in the preferred embodiments. The center of the polymer matrix 82 contains an inflatable balloon 84 which is surrounded by a substantially cylindrical and expandable electrode 86 which could take the form of an expandable wire mesh.

In use, the balloon 84 is inflated through lumen 85 using any appropriate fluid or gas. In its expanded state, as depicted in Figure 8B, electrode 86 expands with balloon 84 and is used to provide current to transport the drugs or fixative contained in the polymer matrix 82 to the surrounding tissue. Electric current is provided to the electrode 86 using wire 87 which runs alongside lumen 85.

Figures 9A and 9B depict an alternate embodiment of a catheter 90 incorporating a balloon 92 and polymer matrix material 94. In this embodiment, the catheter body 96 includes a core 98 extending through the balloon 92, around which the electrode 100 is wrapped in a coil fashion. Catheter body 96 also includes central guide wire lumen 105.

The balloon 92 consists of a substantially cylindrical section of a porous, elastic material which is attached along either end to the catheter body 96 using an adhesive or heat weld. The polymer matrix material 94 is disposed on the outer surface of the balloon 92 for intimate contact with a vessel wall 101 after expansion (see Figure 9B).

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In use, the balloon 92 is expanded with a fluid supplied through fluid-supply lumen 102 while wire lumen 104 houses the wire 106 which supplies current to the electrode. The fluid used to expand the balloon 92 is preferably either water or a weak electrolyte solution to enhance current flow through the polymer matrix material 94 which, in turn, enhances drug delivery to the target tissue.

Figure 10 depicts a catheter substantially similar to the catheter 90 disclosed in Figures 9A and 9B, with the substitution of a transducer 108 for the electrode of catheter 90. The transducer 108 is used to produce sonic energy which moves drug from the polymer matrix material 110 using phonophoresis in the place of iontophoresis. Power is supplied to the transducer 108 using wire 109 which runs through a wire supply lumen.

The preferred fluids used for expansion of the balloon 112 include water or saline, although any fluid used to expand the balloon 112 need only provide the physical properties which enhance the propagation of sonic energy from the transducer 108 to the polymer matrix 110 and, finally, to the target tissue for delivery of the drug.

In addition to the embodiments of Figures 1-10, illustrated principally for delivery of a fixative to a vessel wall, catheters according to the present invention can also be used to deliver any drug to or through a vessel wall. In particular, each of the above embodiments of Figures 1-10 may be used for such drug delivery and each embodiment would be useful for delivering an antitumor, antihyperplastic or other agent through a vessel wall to a nearby or adjacent tumor or other internal body tissue. For example, a drug may be delivered substantially transversely to the longitudinal axis of a body passageway to treat a localized region of tissue located adjacent to the passageway by using iontophoresis to drive through the passageway wall and

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into the surrounding or adjacent tissue. Any of the foregoing alternative embodiments of the apparatus as seen in Figures 1-10 may also be used for such drug delivery.

5 In particular, tumors may be treated by delivering certain drugs through blood vessels or the intestinal tract or whatever to adjacent tumor sites. Further, the present invention is well suited to delivery of sensitizer and immunomodulator drugs.

10 For the purposes of primary or adjuvant treatment or other circumstances where drug delivery to a specific local or regional internal body tissue site such as a solid tumor, abscess, regional lymph nodes or the like is desired, further embodiments of the present  
15 invention as shown in Figure 11 are preferred. The tissue delivery system shown in Figure 11 includes a drug delivery apparatus 120 that is positioned into a specific tissue, such as a tumor.

The preferred drug delivery apparatus 120 for  
20 treating internal body tissue includes a flexible catheter body 121 and substantially cylindrical polymer matrix 124. Positioned in the polymer matrix 124 is an electrode 128 which is connected to wire 130 which extends to the proximal end of the catheter 120.

25 In use, the catheter body 121 is moved into position. The drug is then driven out of the polymer matrix 124 by a voltage gradient (iontophoresis) using electrode 128.

It is to be understood that apparatus 120 can  
30 range in size from very large (trocar) to very small (tenths of mm), depending on the type and location of internal body tissue to be treated.

The embodiment in Figure 11 preferably utilizes  
iontophoresis to drive the drug from the polymer matrix  
35 124. Iontophoresis is preferred because it facilitates both transport of a fixative or drug and enhances tissue penetration. If iontophoresis is used, then similarly

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to the structure seen in Figure 2, the catheter electrode 128 is located within the polymer matrix 124, while the other electrode (not shown) is preferably located on the body of the patient. The other electrode  
5 may also, in certain applications, be positioned at other regions of the patient, including appropriate internal areas and may, in fact, also be located along the catheter body at a site removed from catheter electrode 128.

10 For treatment of an internal body tissue according to the present invention, the introducer (not shown) is placed into the target area, which may be a tumor or the like, after identification of the position of the lesion mechanically, radiographically, thermally,  
15 ultrasonically, or through some other like methodology. The trocar/probe can be designed for steerability to facilitate positioning into the tumor. This can be accomplished by simply placing a bend in the trocar or by other mechanical design techniques known to those  
20 skilled in the art.

The active apparatus 120 is then passed through or over the introducing element directly over the inducer or through the void left in the intervening tissue by the withdrawal of the introducer. After  
25 apparatus 120 is in place, as confirmed by one of the foregoing methods, the active compound is delivered from the polymer matrix 124 into the local or regional tissue. Using an embodiment of apparatus 120 of the type seen in Figure 11, the delivery is accomplished  
30 iontophoretically. The active compounds delivered to an internal body tissue using apparatus 120 include, but are not limited to, antitumor agents such as the vinca alkaloids, anthracycline antibiotics, platinum analogs, antimetabolites (e.g., methotrexate); antibiotics;  
35 sensitizers or other compounds.

The advantage of this method is that it allows delivery of the drug into the interstitial fluid and

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into the cells of the target area themselves even if the vasculature of the area is severely compromised and the cells do not preferentially take up the drug. These phenomena are a well-known attribute of solid tumors and constitute one of the most significant barriers to the treatment of such cancers.

In addition to delivery of antitumor agents to internal tissues, the usefulness of the present apparatus and method for the treatment of other diseases of internal tissue will be appreciated by those skilled in the art.

In the case of both the vascular delivery embodiments (Figs. 1-9) and tissue delivery embodiment (Fig. 11) described herein, phonophoresis (sometimes referred to as sonophoresis) can be used as an alternative to iontophoresis to transport drugs from the polymer matrix into the surrounding tissue.

Phonophoresis is the use of ultrasonic or high frequency sound waves to transport drugs. For certain therapeutic procedures, phonophoresis has several advantages over iontophoresis, including the ability to achieve greater penetration and to more readily deliver an entire molecule, rather than an ionically charged form of the drug. Prior applications of phonophoresis have been limited to transdermal delivery of drugs such as anti-inflammatory agents and local anesthetics through the skin to treat epicondylitis, tendonitis, bursitis and osteoarthritis.

Phonophoresis is also well-suited for driving fixatives or drugs from the polymer matrix material of the present invention to localized body passageways or internal tissues because it facilitates both transport of a fixative or drug from the polymer matrix and enhances tissue penetration. In addition to drug delivery, ultrasound may be advantageously used with the catheter of the present invention based on the increased tissue temperature, tissue hyperemia and increased



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capillary permeability associated with ultrasound. These actions can enhance intra-tissue drug transport and cellular uptake as well as cause vasodilation/relaxation which may be beneficial in vascular drug applications using catheter embodiments of the type described herein.

When phonophoresis is used with either the vascular delivery embodiment or tissue delivery embodiment of the catheter of the present invention, the cathode electrode is replaced by an ultrasonic piezoelectric transducer (barium titanate, lead zirconate titanate, or the like), which is connected to the external power source. After the catheter is in place, the ultrasonic transducer is activated to transport drugs or fixatives into tissue surrounding the catheter.

The diffusion rate of drugs delivered by phonophoresis depends upon the intensity and frequency of the ultrasonic field. Prior transdermal applications of phonophoresis use intensities of 0.1 to 6 watts/cm<sup>2</sup> and involve direct correlation between the amount of drug diffused and the intensity of the ultrasonic field. Internal applications (not requiring transdermal delivery) of phonophoresis with the catheter embodiments of the present invention are envisioned to require significantly less intensity to deliver an equal amount of drug. Various frequencies can be used. A frequency of about 1 MHz has been optimally used in transdermal phonophoresis. It is envisioned that approximately 1 MHz or less can be used for internal applications of the catheter embodiments described herein.

In addition to the substitution of phonophoresis for iontophoresis as described above, an additional feature that can be incorporated in catheters according to the present invention is a protective covering over the polymer matrix material. A protective covering may be useful with some polymer matrix

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materials which are not as dimensionally stable as others and could be particularly sensitive to shearing and/or abrasion during insertion and removal. The shearing and/or abrasion may cause portions of the polymer matrix material to remain in the patient after treatment.

To prevent that occurrence, catheters according to the present invention can be fitted with protective coverings that take a number of forms. One version of a protective covering is depicted in Figures 12A and 12B, where the catheter 132 includes an outer sheath 134 which covers the polymer matrix 136 during insertion of the catheter 132. After the catheter 132 is in position, the sheath 134 is retracted to expose the polymer matrix 136 and drug delivery can proceed (either with expansion of the polymer matrix as depicted in Figure 12B or with delivery of the drug without expansion). After treatment the sheath 134 is then extended to again protect the polymer matrix 136 during removal of the catheter 132.

The sheath 134 in this embodiment of the protective covering is preferably constructed of a rigid material to provide consistent retraction and extension characteristics. An additional advantage of the sheath 134 is that the material used for its construction is also typically impermeable to the drug contained in the polymer matrix 136. That impermeability prevents delivery of the drug in the polymer matrix through passive diffusion to tissue encountered during insertion or removal of the catheter 132, thus enhancing the dosage accuracy of the catheter 132.

An alternate protective covering is depicted in Figure 13, where an outer membrane 144 covers a polymer matrix (not shown) in catheter 140. It will be understood that catheter 140 could take the form of any of the catheters described in detail above. The membrane 144 is porous to the drug contained in the

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polymer matrix to allow transfer through the membrane 144 using either iontophoresis or phonophoresis.

If outer membrane 144 is constructed of a flexible material it can be used in catheters in which the polymer matrix material 142 is expanded with an electrode, transducer, wire basket or inner balloon (all of which are described in detail above). If expandable, the membrane 144 can be loosely fit around the polymer matrix to allow room for expansion. In the alternative, if the membrane 144 is elastic or stretchable, its fit around the polymer matrix can be tighter as the membrane can then stretch around the expanded polymer matrix.

As with the rigid retractable sheath, the porous membrane 144 also protects the polymer matrix from shearing and abrasion and also offers some degree of protection from passive diffusion during insertion and removal of the catheter 140 (although the membrane 144 is porous by its very nature).

It will also be understood that portions of the membrane 144 can be impermeable (non-porous) to further control delivery of the drug in the polymer matrix. In particular, the impermeable portions would preferably be located on either end of the membrane 144 to limit or prevent drug delivery in an axial direction along the body of the catheter 140. This design is particularly useful in expanding catheters, as after expansion of the polymer matrix and associated membrane 144, the porous portions of the membrane 144 would be in intimate contact with the vessel wall or target tissue, while the remaining sections of membrane 144 which are not in intimate contact would be impermeable, thereby limiting unwanted drug transfer in the axial direction.

Although the description of the preferred embodiments and methods have been quite specific, it is contemplated that various modifications could be made without deviating from the spirit of the present invention. Accordingly, it is intended that the scope

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of the present invention be dictated by the appended claims, rather than by the description of the preferred embodiments and methods.

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## WE CLAIM:

1. A drug delivery apparatus having a distal end  
and a proximal end for local delivery of a drug to  
5 internal body tissue comprising:
  - (a) a flexible catheter for insertion into an  
internal target area of a body;
  - (b) drug delivery means connected said catheter  
proximate said distal end of said drug delivery  
10 apparatus for delivering a drug to said target  
area, said drug delivery means comprising a  
polymer matrix retaining said drug; and
  - (c) transport means for actively transporting said  
drug from said polymer matrix to said internal  
15 target area of a body.
2. The drug delivery apparatus of claim 1, wherein  
said polymer matrix is coaxially aligned about a  
longitudinal axis of said catheter body.  
20
3. The drug delivery apparatus of claim 1, wherein  
said catheter body includes an integral introducer.
4. The drug delivery apparatus of claim 1, wherein  
25 said transport means comprises iontophoresis means.
5. The drug delivery apparatus of claim 4, wherein  
said iontophoresis means comprises an electrode  
located within said polymer matrix.  
30
6. The drug delivery apparatus of claim 1, wherein  
said transport means comprises phonophoresis means.
7. The drug delivery apparatus of claim 6, wherein  
35 said phonophoresis means comprises an ultrasonic  
transducer located within said polymer matrix.

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8. The drug delivery apparatus of claim 1, further comprising expansion means for expanding said drug delivery means in a direction substantially radial to said catheter body.
- 5 9. The drug delivery apparatus of claim 8, wherein said expansion means comprises a wire basket biased in an expanded configuration.
- 10 10. The drug delivery apparatus of claim 8, wherein said expansion means comprises a wire basket biased in a relaxed position.
11. The drug delivery apparatus of claim 8, wherein  
15 said expansion means comprises a balloon.
12. The drug delivery apparatus of claim 1, further comprising protective means for protecting said polymer matrix from physical degradation during insertion and  
20 removal of said apparatus.
13. The drug delivery apparatus of claim 12, wherein said protective means further comprises a movable sheath.
- 25 14. The drug delivery apparatus of claim 12, wherein said protective means further comprises a porous membrane covering said polymer matrix.
- 30 15. A drug delivery apparatus for local delivery of a drug to an internal body passageway having an elongated passageway wall comprising:  
(a) a flexible catheter having a distal end and a proximal end;  
35 (b) drug delivery means connected said catheter proximate said distal end of said drug delivery apparatus for delivering a drug to said target

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area, said drug delivery means comprising a polymer matrix retaining said drug;

(c) transport means for actively transporting said drug from said polymer matrix to said internal target area of a body; and

(d) expansion means for expanding said drug delivery means in a direction substantially radial to said catheter body.

10 16. A method of delivering a drug to an internal target area of a body, said method comprising the steps of:

15 (a) inserting a distal end of a catheter into said body proximate said internal target area, said catheter including a polymer matrix proximate said distal end, said polymer matrix retaining said drug; and

20 (b) transporting said drug from said polymer matrix to said internal target area of a body using transport means for actively transporting said drug, said transport means proximate said distal end of said catheter.

25 17. The method of claim 16, wherein the step of transporting further comprises iontophoretically transporting said drug.

30 18. The method of claim 16, wherein the step of transporting further comprises phonophoretically transporting said drug.

35 19. The method of claim 16, further comprising the step of expanding said polymer matrix in a direction substantially radial to a longitudinal axis of said catheter.

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20. The method of claim 16, further comprising the step of protecting said polymer matrix from physical degradation during said step of inserting.

5 21. A method of delivering a drug to an internal target area of a body, said method comprising the steps of:

- 10 (a) inserting a distal end of a catheter into said body proximate said internal target area, said catheter including a polymer matrix proximate said distal end, said polymer matrix retaining said drug;
- 15 (b) expanding said polymer matrix in a direction substantially radial to a longitudinal axis of said catheter; and
- 20 (c) transporting said drug from said polymer matrix to said internal target area of a body using transport means for actively transporting said drug, said transport means proximate said distal end of said catheter.



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FIG. 1

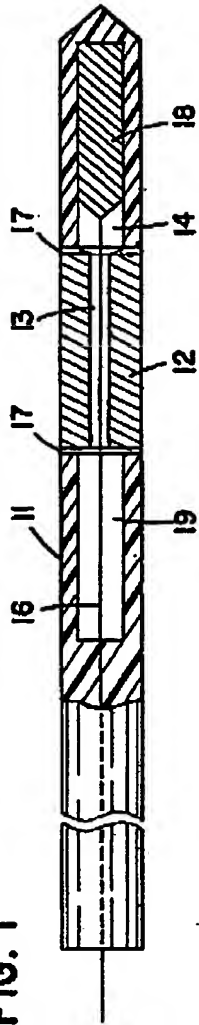


FIG. 2

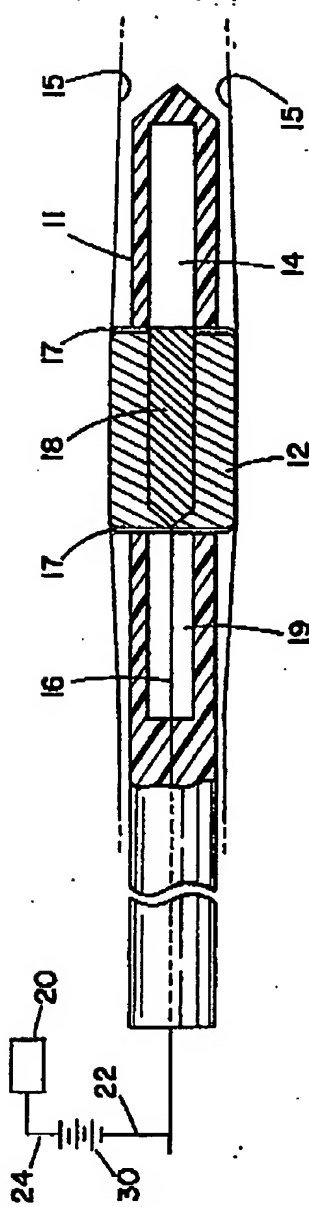
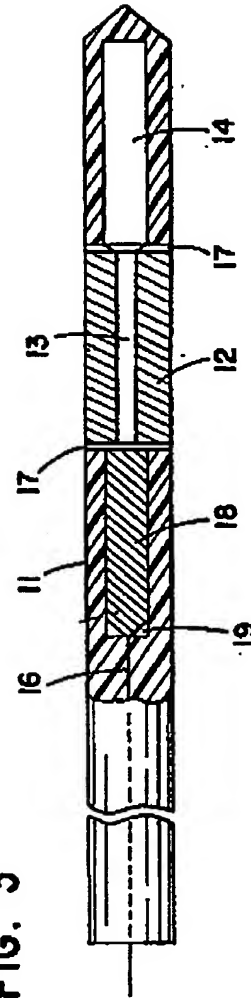


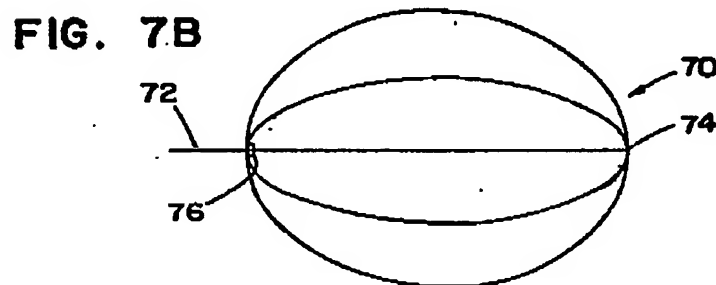
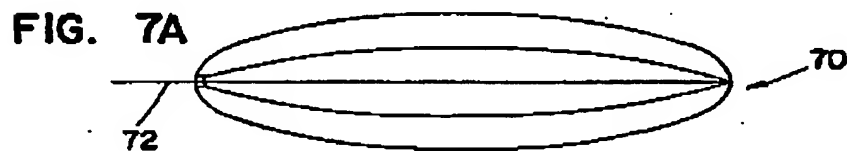
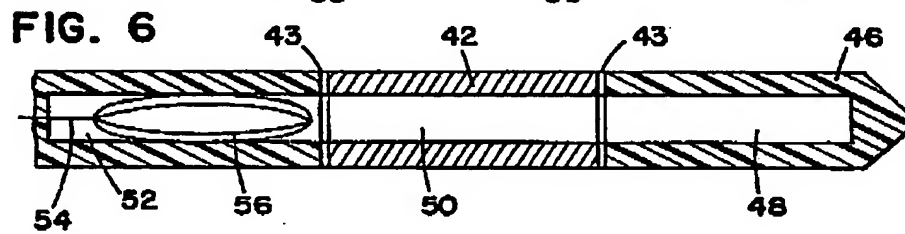
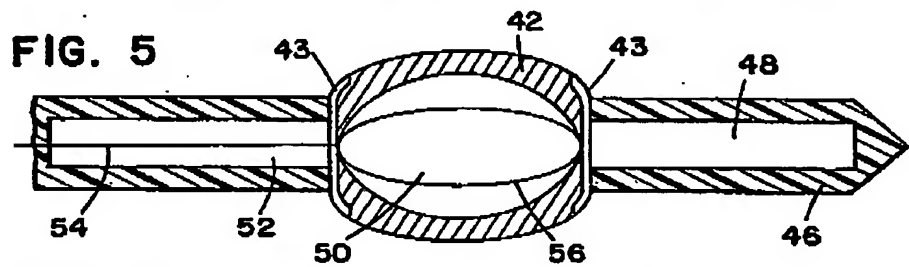
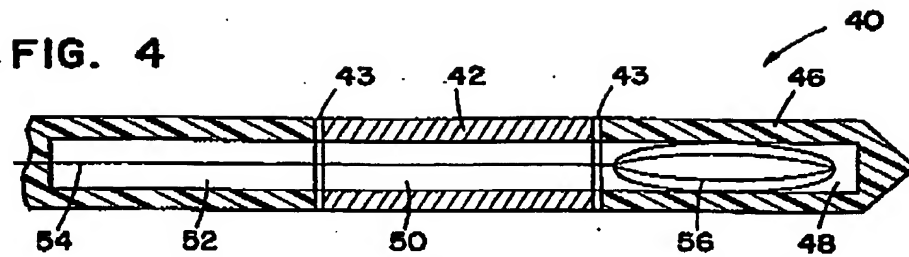
FIG. 3



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FIG. 8A

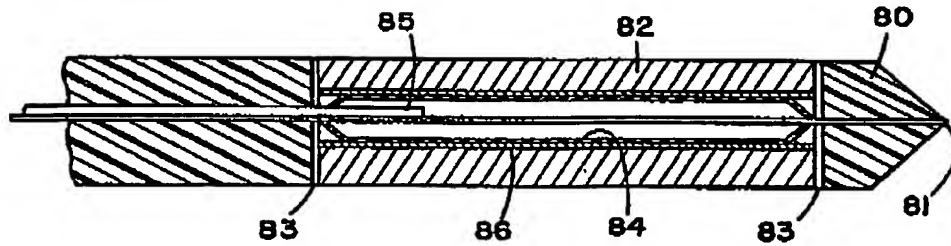


FIG. 8B

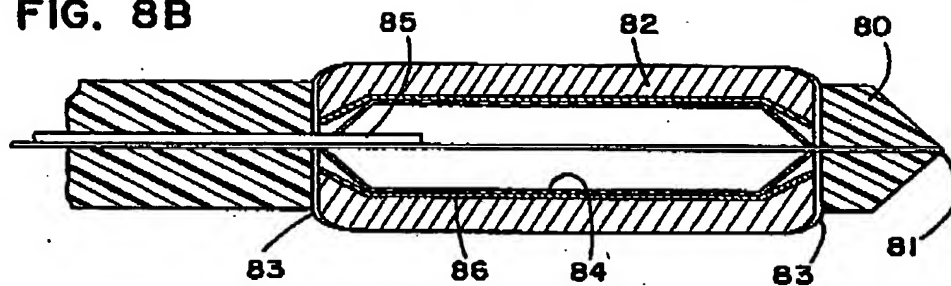


FIG. 9A

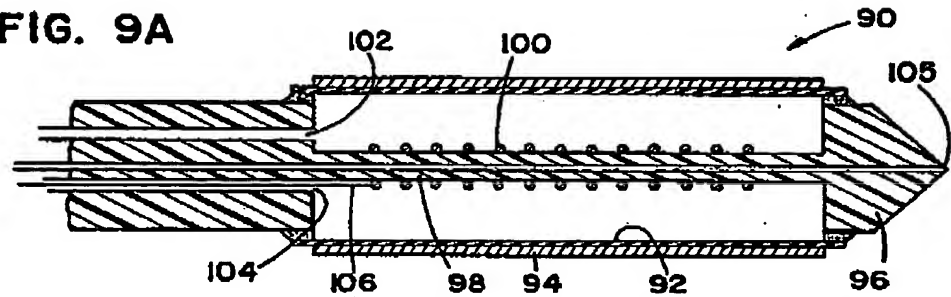
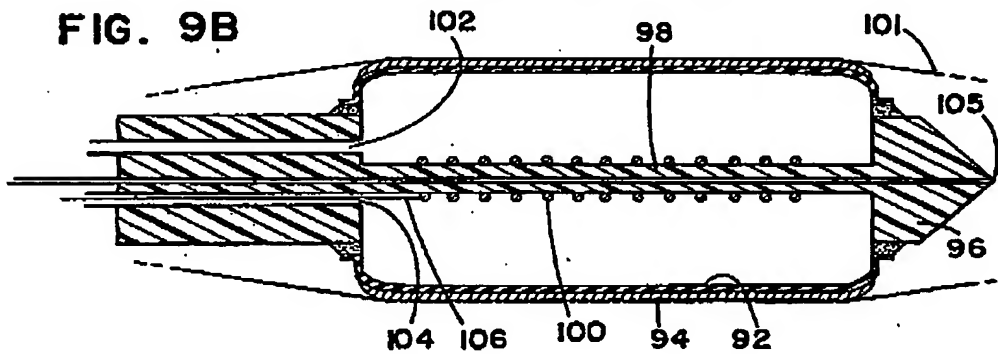


FIG. 9B



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FIG. 10

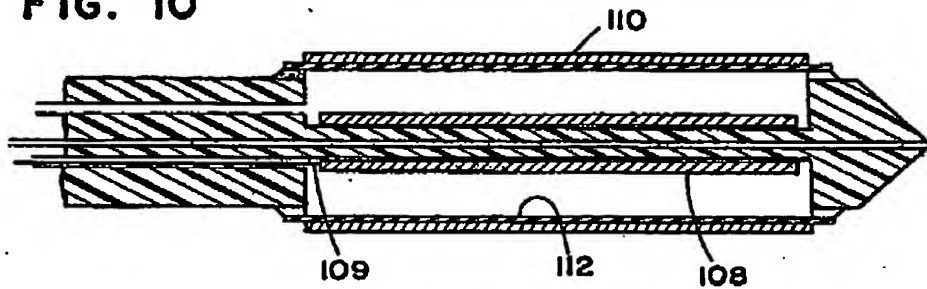


FIG. 11

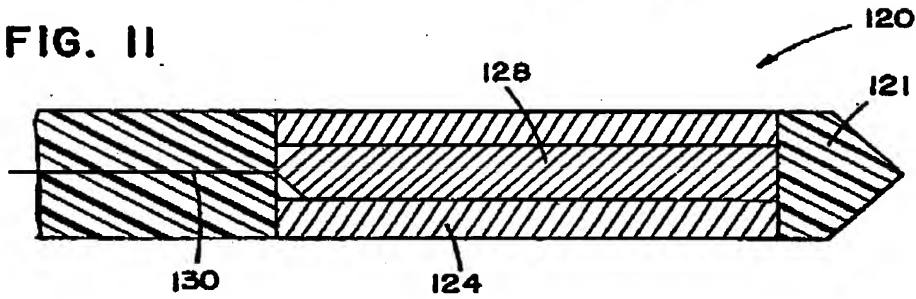


FIG. 12A

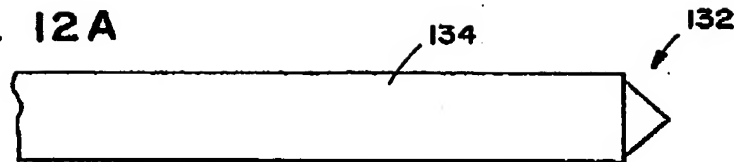


FIG. 12B

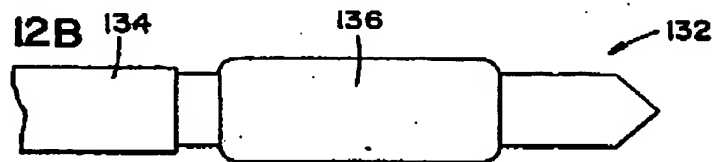
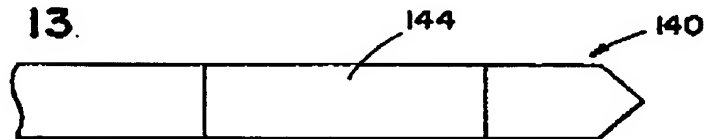


FIG. 13



## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 92/10839

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC <sup>5</sup> : A 61 M 25/00, A 61 N 1/30, A 61 M 29/02, A 61 M 25/10		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC <sup>5</sup>	A 61 M, A 61 N	
Documentation Searched other than Minimum Documentation to the extent that such documents are included in the fields searched *		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> *		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
Y	WO, A1, 91/19 529 (CORTAK) 26 December 1991 (26.12.91), fig. 1, 6, 8-10; page 9, line 33, page 16, line 27 - page 17, line 33; page 18, line 23 - page 19, line 10; page 21, line 41 - page 23, line 10; page 25, line 3 - page 26, line 23.	1, 2, 4, 6, 8, 11, 15
A	---	3
Y	US, A, 4,663 358 (S.H. HYON et al.) 05 May 1987 (05.05.87), column 1, lines 7-19; column 3, line 61 - column 4, line 2.	1, 2, 4, 6, 8, 11, 15
A	---	1, 2, 4, 5, 12, 14, 15
A	US, A, 5 041 107 (R.W. HEIL) 20 August 1991 (20.08.91).	1, 2, 4, 5, 12, 14, 15
<p>* Special categories of cited documents: **</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"Z" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
09 April 1993	29 APR 1993	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	LUDWIG e.h.	

Form PCT/ISA/210 (second sheet) (January 1985)

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International Application No PCT/US 92/10839

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, * with indication, where appropriate, of the relevant passages	Relevant to Claim No.
	the whole document; especially column 4, lines 31-53; column 4, line 64 - column 5, line 10.	
A	DE, C1, 3 915 636 (W. SASS et al.) 26 April 1990 (26.04.90), the whole document; especially column 2, lines 31-33; claims 1,5.	1,4,8, 11,15
A	US, A, 4 582 181 (W.J. SAMSON) 15 April 1986 (15.04.86), abstract -(cited in the application).	3

Form PCT/ISA 210 (extra sheet) (January 1985)

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/ 10839

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-21  
because they relate to subject matter not required to be searched by this Authority, namely:  
See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

**ANHANG**

zum internationalen Recherchen-  
bericht über die internationale  
Patentanmeldung Nr.

In diesen Anhang sind die Mitglieder  
der Patentfamilien der in obenge-  
nannten internationalen Recherchenbericht  
angeführten Patentdokumente angegeben.  
Diese Angaben dienen nur zur Unter-  
richtung und erfolgen ohne Gewähr.

**ANNEX**

to the International Search  
Report to the International Patent  
Application No.

PCT/US 92/10839 SAE 68324

This Annex lists the patent family  
members relating to the patent documents  
cited in the above-mentioned inter-  
national search report. The Office is  
in no way liable for these particulars  
which are given merely for the purpose  
of information.

**ANNEXE**

au rapport de recherche inter-  
national relatif à la demande de brevet  
international n°

La présente annexe indique les  
membres de la famille de brevets  
relatifs aux documents de brevets cités  
dans le rapport de recherche inter-  
national visée ci-dessus. Les renseigne-  
ments fournis sont donnés à titre indica-  
tif et n'engagent pas la responsabilité  
de l'Office.

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9119529	26-12-91	AU A1 80745/91 EP A1 533816	07-01-92 31-03-93
US A 4663358	05-05-87	JP A2 61252261	10-11-86
US A 5041107	20-08-91	keine - none - rien	
DE C1 3915636	26-04-90	EP A2 396945 EP A3 396945 US A 5047028	14-11-90 13-03-91 10-09-91
US A 4582181	15-04-86	US A 4730616 US E 33166	15-03-88 20-02-90